REMARKS

The fee for filing a three month extension of time should be charged to Deposit Account No. 02-1818. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 02-1818. If a Petition for extension of time is needed, this paper is to be considered such Petition.

A supplemental Information Disclosure Statement is filed under separate cover on the same day herewith. Attached as an Appendix are:

1. Figure depicting sequence alignment of IFN-alpha polypeptides;
2. Annotated paper copy of SEQ ID NO:232;
3. Replacement Sequence Listing on compact disc (labeled Replacement Copy #1 and Replacement Copy #2);
4. Computer-readable copy of substitute Sequence Listing; and
5. Verified Statement Pursuant to §1.821(f).

Claims 1, 5-8, 21-23, 40, 46, 137, 279, 307 and 341, 343, 345 and 347-356 are pending in the application. Claims 1, 5-8, 21, 23, 46, 279, 307, 341, 347 are amended and claims 9-19, 43, 44, 47-74, 139-144, 306, 308, 315, 316, 332-340, 342, 344, 346 are cancelled without prejudice, and claims 348-356 are added to focus prosecution on modified interferon alpha molecules that contain a mutation at E41Q in order to advance such claims to allowance. Interferon alpha with the E41Q is in phase I clinical trials for subcutaneous administration; and in the IND stage for oral administration. Cancelled subject matter will be pursued in further continuing applications. for clarity and consistency, claim 138 is cancelled without prejudice or disclaimer, and claims 346 and 347 are added. No new matter is added. Non-elected and withdrawn subject matter is retained pending allowance of a linking claim.

The specification is amended to correct SEQ ID No. 232, which sets forth the sequence of the known and commercially available consensus sequence interferon alpha to correct an inadvertant typographical error. The interferons encoded by the different genes and alleles are highly conserved. A sequence alignment depicting the sequences of a variety of IFN-alpha polypeptides, whose sequences are included in the instant application, is attached to this response. In the alignment, the SEQ ID NOS are specified, with the species of interferon indicated in the adjacent parenthesis. The alignment shows that the IFN-alpha species exhibit a high degree of sequence identity. For example, in the Sequence Alignment, IFN-alpha 2b is highlighted in green and corresponding residues in other IFN-alpha species that are different are highlighted in yellow. As the alignment shows, position E41 in IFN-alpha 2b aligns with position E41 in each of the IFN-alpha species (highlighted in gray in the Figure). Position E41 in IFN-alpha 2b also aligns with consensus IFN-alpha, as evidenced

by the disclosure of the instant specification, which identifies position 41 as a corresponding position in consensus IFN-alpha (see e.g., pages 91, line 18 to page 94, line 6). It appears, however, that SEQ ID NO:232 as set forth in the Sequence Listing of the instant application contains a typographical error because the amino acid at position 38 in advertently was not included. The sequence of consensus IFN-alpha is well known in the art (see e.g., U.S. Patent Serial Nos. 4,897,471 and 4,695,623) and contains a Phe (F) at position 38. The substitute Sequence Listing and amendment herein corrects this obvious typographical error.

CLAIM OBJECTIONS

Claims 5-7, 23, 43, 279, 307-308, 341, 342, 344, 346, 347 and the dependent claims are objected as containing non-elected subject matter. As noted previously, withdrawn subject matter is retained pending allowance of a generic claim. All pending claims are directed to modified interferon alpha cytokines that contain a replacement of E with Q at residue 41. As discussed above and evidenced in the attached figure depicting the alignment among the members of this family, the interferon alpha family of polypeptides constitutes a closely related family of polypeptide allelic variants (IFN-α2a, 2b and 2c) and closely related polypeptides (See attached figure).

Claims 340 and 347 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. While not conceding the propriety of this rejection, claim 340 is cancelled herein.

Analysis

The Examiner, however, is reminded that a dependent claim does not have to further limit the claim from which it depends, but rather must include all limitations in the claim from which it depends. As stated in MPEP (608.01(n), the test for a proper dependent claim is:

> **Whether the dependent claim includes every limitation of the parent claim. The test is <u>not</u> whether the claims differ in scope. A proper dependent claim shall not conceivably be infringed by anything which would not also infringe the basic claim.**

A dependent claim does not lack compliance with 35 U.S.C. 112, fourth paragraph, simply because there is a question as to (1) the significance of the further limitation added by the dependent claim, or (2) whether the further limitation in fact changes the scope of the dependent claim from that of the claim from which it depends. The test for a proper dependent claim under the fourth paragraph of 35 U.S.C. 112 is whether the dependent

claim includes every limitation of the claim from which it depends. The test is not one of whether the claims differ in scope. [see MPEP 608.01(n)].

Thus, previously pending claim 340 and currently pending claim 347 are properly dependent as they include every limitation of the base claim. Claim 347 recites:

> **The interferon alpha cytokine of claim 1, comprising two amino acid replacements.**

Claim 1 is directed to interferon alpha cytokines that contain an amino acid modification. A cytokine that contains two amino acid modifications also contains one amino acid modification. Therefore, claim 347 includes all limitations of the base claim.

DECLARATION OF DR. VEGA

. The Examiner states that the executed declaration under 37 C.F.R. §1.132 of Dr. Manuel Vega, filed on 10/09/2007, was considered and that it presents facts that indicate that the mutant E41Q of the IFN alpha-2b has increased protease resistance, in vitro and in vivo, anti-proliferative and anti-viral activity, with respect to the IFN alpha-2b, which does not posses this modification. The Examiner further states that "[t]he declaration was not necessitated by any rejection made by the Office."

Applicant agrees that a DECLARATION showing results not taught or suggested is not needed. This is because the Office has failed to set forth a *prima facie* case of obviousness over the any art. Nevertheless, in the interest of advancing claims to this valuable product to allowance, Applicant provided the DECLARATION to show that by virtue of an E to Q replacement at position 41, interferon-alpha cytokines possess properties that are not taught or suggested by the cited art. As described in the DECLARATION, the results show that the exemplary mutant E41Q not only exhibits increased protease resistance to a cocktail of proteases, but also to blood lysate, serum and to chymotrypsin. Thus, the amino acid replacement confers increased protease resistance of the cytokine across the entire molecule, which increased resistance is not specific to a particular protease.

In the DECLARATION, data also are provided that demonstrate that the proteins exhibit improved pharmacokinetics upon *subcutaneous and oral administration* compared to proteins not containing the amino acid replacement(s). For example, the DECLARATION provides data demonstrating that a mutant IFN-alpha containing only a single amino acid mutation (E41Q), when administered subcutaneously or orally, retains anti-viral activity in the serum for a longer time period than the native polypeptide. In addition, the result show that SuperLEADs, containing two or more amino acid changes described in the above-captioned application, also exhibit similar increases in half-life. Thus, an IFN-alpha,

containing in many instances only a single amino acid replacement to render the cytokine protease resistance, can be used as a therapeutic due to the improved properties compared to the native polypeptide.

With respect to per-oral administration, the native polypeptide exhibits **NO** detectable activity when administered orally; whereas, the IFN-α with a single amino acid change, can be successfully administered orally.

None of the cited art, singly or in any combination, teaches or suggests that modification of this locus results in substantial increase in resistance to proteases, retention of biological activity and improved pharmacokinetics when administered subcutaneously and orally. Further none teaches or suggests that, by virtue of this change interferon-alpha cytokines can be administered orally and exhibit activity; whereas interferon-alpha cytokines that do not contain this modification do not exhibit any activity upon oral administration. The DECLARATION shows that a single change from E to Q at position 41 in an interferon alpha renders improves the pharmacokinetics upon subcutaneous administration and also permits the protein to be formulated, for example, as tablet or capsule for oral administration. No art of record even suggests that rendering a protein protease resistant by virtue of changes in its primary sequence permits oral delivery nor the improved properties observed upon subcutaneous administration. The cited art does not teach, suggest or even hint at such extraordinary results. If the art suggests anything, it suggests that IFN-alphas contain a plurality of sites that are cleaved by proteases. Hence, as discussed below in addressing the rejection under 35 U.S.C. §103(a), the DECLARATION is sufficient to rebut any *prima facie* case of obviousness of the instant claims.

THE REJECTION OF CLAIMS 1, 6, 17, 279, 341 AND 347 UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1, 6, 17, 279, 341 and 347 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

Paragraph 2 of section 112 requires that the "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the

applicant regards as his invention." Courts have recognized since the requirement that one's invention be distinctly claimed became part of the patent law in 1870, the primary purpose of the requirement is "to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights." General Electric Co. v. Wabash Appliance Corp., 304 U.S. 364, 369 (1938). See, e.g., McClain v. Ortmayer, 141 U.S. 419, 424 (1891) ("The object of the patent law in requiring the patentee [to distinctly claim his invention] is not only to secure to him all to which he is entitled, but to apprise the public of what is still open to them."); Rengo Co. v. Molins Mach. Co., 657 F.2d 535, 551 (3d Cir.) ("Its purpose is to demarcate the boundaries of the purported invention, in order to provide notice to others of the limits beyond which experimentation and invention are undertaken at the risk of infringement.") (internal quotation omitted), cert. denied, 454 U.S. 1055 (1981); Hoganas AB v. Dresser Indus., 9 F.3d 948, 951, 28 USPQ2d 1936, 1939 (Fed. Cir. 1993) (function of claims is "putting competitors on notice of the scope of the claimed invention").

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite. Rosemount Inc. v. Beckman Intstruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983).
The purpose of 35 U.S.C. §112, second paragraph, is to provide those who would endeavor, in future enterprise, to approach the area circumscribed by the claims of a patent, with adequate notice demanded by due process of law, so that they may readily and accurately determine the boundaries of protection involved, evaluate the possibility of infringement and dominance by determining the metes and bound of protection so one can evaluate the possibility of infringement with a reasonable degree of certainty. In re Hammack, 427 F.2d 1378, 166 USPQ 204 (CCPA 1970).

Furthermore, claims are not to be read in a vacuum, and the limitations therein are to be interpreted in light of the specification, giving them their broadest reasonable interpretation.

Analysis

1. Claim 1 is rejected as indefinite because it is unclear whether "one or two replacements could mean an unlimited number of substitutions so that the essential motifs and regions that define the IFN alpha are no longer present. Hence, the meets and bounds of the claim could not be determined."

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite. In this instance, the claim recites:

> An isolated interferon (IFN) alpha cytokine, comprising an amino acid replacement in its sequence of amino acids, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the amino acid replacement; wherein an amino acid replacement is E41Q in the interferon-alpha cytokine.

Thus, the claim is directed to an IFN alpha cytokine that contains a change at residue 41 of E to Q. The specification clearly describes the members of the alpha interferon family. Further, such family is well known and is highly conserved. One of skill in the art would know when they had an interferon alpha, and would be able to determine the sequence to whether position 41 was a "Q."

To evidence that one of skill in the art would knows what interferon alpha is, a search of issued and published applications prior to the earliest priority date claimed in this application was conducted in the full text MicroPatent database. The following is a list of the hits, with some exemplary claims selected at random:

© 1998 MicroPatent
Search scope: US Granted US Applications; Claims
Years: 1971-2008
Text: interferon adj3 alpha Issue/Publication Date: 19710101 to 20010824
103 patents selected (of 103 matches).

1. US6265214 B1 A61K 20010724 Board of Regents, The University of Texas System
   Methods and compositions for inducing monocyte cytotoxicity
   Claim 1:A method of generating a continuous cell line which produces a factor capable of inducing human monocytes to a cytotoxic state, the method comprising the steps of: (a) immortalizing human T-cells to produce continuous cell clones; (b) identifying a clone which produces a factor having the following characteristics: i. capability of inducing human monocytes to a cytotoxic state; ii. retention of biological activity following treatment at pH 2 for one hour; iii. retention of biological activity following treatment at 60° C. for one hour; iv. ability to bind to Matrex Gel Red A under low-salt conditions and elute from Matrex Gel Red A under high-salt conditions; and v. retention of biological activity in the presence of anti-serum to interferon gamma, **interferon alpha**, or a combination of anti-sera to interferon alpha and gamma; and (c) culturing the clone to produce the continuous cell line.
2. US6277830 B1 C07H 20010821 Schering Corporation
   5'-amino acid esters of ribavirin and the use of same to treat hepatitis C with interferon
3. US6248363 B1 A61K 20010619 Lipocine, Inc.
   Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
4. US6235498 B1 C07K 20010522 Genentech, Inc.

Method for culturing recombinant cells

5. US6250469 B1 A61K 20010626 Schering Corporation
Formulations for protection of peg-interferon alpha conjugates
Claim 1: An article of manufacture, comprising a container containing a lyophilized powder produced by lyophilizing a solution comprising **PEG-interferon alpha** conjugates, a buffer, a stabilizer, a cryoprotectant and a solvent, wherein said buffer is sodium phosphate, said stabilizer is a poly(oxy-1,2-ethanediyl), said cryoprotectant is sucrose and said solvent is water.
6. US6177074 B1 A61K 20010123 Schering Corporation
Polyethylene glycol modified interferon therapy
7. US6180096 B1 A61K 20010130 Schering Corporation
Formulations for protection of peg-interferon alpha conjugates
8. US6172046 B1 A61K 20010109 Schering Corporation
Combination therapy for eradicating detectable HCV-RNA in patients having chronic Hepatitis C infection
9. US6165502 A A61K 20001226 Albany Medical College|Medical College of New Jersey
Protein-lipid vesicles and autogenous vaccine comprising the same
10. US6130200 A A61K 20001010 Alza Corporation
Gel composition and methods
11. US6063772 A A61K 20000516 ICN Pharmaceuticals, Inc.
Specific modulation of Th1/Th2 cytokine expression by ribavirin in activated T-lymphocytes
12. US6051256 A A61K 20000418 Inhale Therapeutic Systems
Dispersible macromolecule compositions and methods for their preparation and use
13. US6042822 A A61K 20000328 Enzon, Inc.
Interferon polymer conjugates
14. US6083921 A A61K 20000704 XU; KAI JIAN
Pharmaceutical compositions and method of using same
15. US6036949 A A61K 20000314 Amarillo Biosciences, Inc.
Treatment of fibromyalgia with low doses of interferon
16. US6028243 A C12N 20000222 The Cleveland Clinic Foundation
Mice and cells with a homozygous disruption in the RNase L gene and methods therefore
17. US6004549 A A61K 19991221 Schering Corporation
Crystalline protein controlled release compositions
18. US6004944 A C12N 19991221 The Regents of the University of California
Protein delivery by secretory gland expression
19. US5993851 A A61K 19991130 PharmaDerm Laboratories, Ltd.
Method for preparing biphasic multilamellar lipid vesicles
20. US5951974 A A61K 19990914 Enzon, Inc.
Interferon polymer conjugates
21. US5985263 A A61K 19991116 Enzon, Inc.
Substantially pure histidine-linked protein polymer conjugates
22. US5972331 A A61K 19991026 Schering Corporation
Crystalline interferon alpha for pulmonary delivery and method for producing the same
23. US5968735 A C12N 19991019 Max Delbruck Centrum fur Molekular Medizin Berlin
Vector for the expression of therapy-relevant genes
24. US5958402 A A61K 19990928 University of Florida
Antitumor therapy using ovine or bovine interferon-tau
25. US5942223 A A61K 19990824 University of Florida
Antiviral therapy using ovine or bovine interferon-tau
26. US5902799 A A61K 19990511 The Trustees of the University of Pennsylvania

Methods of modulating tissue growth and regeneration

27. US5935940 A A61K 19990810 Trustees of the University of Pennsylvania

Compositions and methods for modulating growth of a tissue in a mammal

28. US5910304 A A23K 19990608 Texas A&M University System

Low-dose oral administration of interferons

29. US5908621 A A61K 19990601 Schering Corporation

Polyethylene glycol modified interferon therapy

30. US5886006 A C07D 19990323 Minnesota Mining and Manufacturing Company

Fused cycloalkylimidazopyridines

31. US5882640 A A61K 19990316 The Texas A&M University System

Treatment of hyperallergenic response with oral interferon

32. US5846526 A A61K 19981208 The Texas A&M University System

Treatment of autoimmune disorders with oral interferon

33. US5866341 A C12N 19990202 Chugai Pharmaceutical Co., Ltd.

Compositions and methods for screening drug libraries

34. US5853755 A A61K 19981229 PharmaDerm Laboratories Ltd.

Biphasic multilamellar lipid vesicles

35. US5846928 A A61K 19981208 PasKen Products Co. , Ltd.

Method for treating cancer patients

36. US5817307 A A61K 19981006 The Texas A&M University System

Treatment of bacterial infection with oral interferon-α

37. US5834594 A A61K 19981110 Hoffman La Roche Inc.

Polyethylene-protein conjugates

38. US5834015 A A61K 19981110 Albany Medical College|University of Medicine and Dentistry of New Jersey

Protein-lipid vesicles and autogenous vaccine comprising the same

39. US5831023 A A61K 19981103 Genentech, Inc.

Recombinant animal interferon polypeptides

40. US5827694 A C07K 19981027 Genentech, Inc.

DNA encoding non-human animal interferons, vectors and hosts therefor, and recombinant production of IFN polypeptides

41. US5762923 A A61K 19980609 Hoffmann La Roche Inc.

Stabilized interferon alpha solutions

42. US5750373 A C07K 19980512 Genentech, Inc.

Enrichment method for variant proteins having altered binding properties, M13 phagemids, and growth hormone variants

43. US5738846 A A61K 19980414 Enzon, Inc.

Interferon polymer conjugates and process for preparing the same

44. US5780220 A A61K 19980714 Trustees of the University of Pennsylvania

Methods and compositions for inhibiting HIV replication

45. US5780279 A C12N 19980714 Genentech, Inc.

Method of selection of proteolytic cleavage sites by directed evolution and phagemid display

46. US5766864 A C12N 19980616 Sumitomo Pharmaceuticals Company, Ltd.

Method of measuring interferon acitivity

47. US5741485 A A61K 19980421 Schering Corporation

Method for preparing zinc interferon alpha-2 crystals

48. US5711944 A A61K 19980127 Enzon, Inc.

Interferon polymer conjugates

49. US5736154 A A61M 19980407 Fuisz Technologies Ltd.

Transdermal delivery system

50. US5731193 A C07K 19980324 Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo

Recombinant DNA and transformant containing the same

Claim 1. A replicable recombinant DNA molecule comprising a plasmid vector, an **interferon-alpha** promoter, and a DNA encoding a polypeptide excluding interferon-alpha, said interferon-alpha promoter and said DNA

being operably linked as an insertion in said plasmid vector, said recombinant DNA molecule capable of expressing an increased amount of said polypeptide in a mammalian host cell when simultaneously or successively stimulated with an interferon-alpha inducer and **an interferon-alpha**, said mammalian host cell producing said polypeptide along with **interferon-alpha** when said mammalian host cell is an interferon-alpha producing cell.

51. US5725850 A A61K 19980310 Chiron Corporation
Use of CSF-1 to treat tumor burden
52. US5656289 A A61K 19970812 Patralan Limited
Pharmaceutical formulations that have a biologically active hydrophilic phase and a chylomicra-containing hydrophobic phase
53. US5654008 A A61K 19970805 Alkermes Controlled Therapeutics Inc. II
Preparation of biodegradable microparticles containing a biologically active agent
54. US5635175 A A61K 19970603 Chiron Corporation
Use of CSF-1 to treat viral infections
55. US5602232 A A61K 19970211 Schering Corporation
Method for producing metal-interferon-α crystals
56. US5587300 A C07K 19961224 Wisconsin Ulumni Research Foundation
Method to increase regulatory molecule production
57. US5529915 A A61K 19960625 Sterling Winthrop Inc.
Lyophilized polyethylene oxide modified protein and polypeptide complexes with cyclodextrin
58. US5516515 A A61K 19960514 Interferon Sciences, Inc.
Separation of alpha interferon receptor proteins and antibodies therefor
59. US5444065 A A61K 19950822 Minnesota Mining and Manufacturing Company
Fused cycloalkylimidazopyridines as inducer of interferon α biosynthesis
60. US5460956 A A61K 19951024 Schering Corporation
Method for preparing interferon alpha-2 crystals
61. US5441734 A A61K 19950815 Schering Corporation
Metal-interferon-alpha crystals
62. US5434249 A C07K 19950718 Viragen Inc.
Method for modulating specific activity of inteferon alpha
63. US5362490 A A61K 19941108 Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo
Human myelomonocyte interferon-gamma, and process for preparation and use thereof
64. US5256560 A A61K 19931026 University of Saskatchewan
Primitive cell colony stimulating factors and lymphohematopoietic progenitor cells
65. US5292642 A A61K 19940308 Board of Regents, The University of Texas System
Methods and compositions for the detection of monocyte cytotoxicity inducing factor
66. US5286482 A A61K 19940215 Board of Regents, The University of Texas System
Methods and compositions for inducing monocyte cytotoxicity
67. US5223408 A A61K 19930629 Genentech, Inc.
Method for making variant secreted proteins with altered properties
68. US5215741 A A61K 19930601 Amarillo Cell Culture Company, Incorporated
Method for prevention of parasite infections
69. US5112948 A A61K 19920512 JONES C MICHAEL
Methods and compositions for inducing monocyte cytotoxicity
70. US5049378 A A61K 19910917 Ciba Geigy Canada Ltd.

Prevention and treatment of porcine haemophilus pneumonia (PHP)

71. US4997646 A A61K 19910305 University of Florida Research Foundation, Inc.|Currators of the University of Missouri
Use of interferons of the alpha family to enhance fertility in mammals

72. US5019382 A A61K 19910528 The Texas A&M University System
Treatment of immuno-resistant disease with low-dose interferon

73. US5028422 A A61K 19910702 Schering Corporation
Treatment of basal cell carcinoma intralesionally with recombinant human alpha interferon

74. US5026544 A A61K 19910625 Board of Reagents, The University of Texas System
Methods and compositions for inhibiting the growth of neoplastic cells

75. US5017371 A A61K 19910521 Amarillo Cell Culture Company, Incorporated
Method for reducing side effects of cancer therapy

76. US5010003 A C12N 19910423 Genentech, Inc.
Use of yeast homologous signals to secrete heterologous proteins

77. US5002878 A A61K 19910326 Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo
Novel lymphokine, monoclonal antibody specific to the lymphokine, and their production and uses

78. US4994556 A A61K 19910219 Kabushiki Kaisha Hayashibara Seibutsu Kagaku
Novel lymphokine and its production and uses

79. US4977245 A A61K 19901211 Board of Regents, The University of Texas System
Methods and compositions for inducing monocyte cytotoxicity

80. US4929442 A A61K 19900529 Exovir, Inc.
Compositions suitable for human topical application including a growth factor and/or related materials

81. US4925919 A A61K 19900515 MERTELSMANN ROLAND|WELTE KARL|VENUTA SALVATORE
Purified interleukin 2

82. US4902618 A G01N 19900220 Wadley Technologies, Inc.
Production of hybridoma antibodies for interferon

83. US4917887 A C07K 19900417 Boehringer Ingelheim International GmbH
Hybrid interferons, their use as pharmaceutical compositions and as intermediate products for the preparation of antibodies and the use thereof and processes for preparing them

84. US4861720 A A61K 19890829 Regents of the University of California
Oncornavirus vaccines and feline alpha-type interferon

85. US4847079 A A61K 19890711 Schering Corporation
Biologically stable interferon compositions comprising thimerosal

86. US4824674 A A61K 19890425 Thomae, Karl
Stable alpha-interferon dosage forms

Claim 1: **Alpha-interferon** dosage form comprising a non-lyophilized dry film of acid-stabilized α -interferon, and an inert carrier supporting said film.

87. US4820514 A A61K 19890411 Texas A&M University System
Low dosage of interferon to enhance vaccine efficiency

88. US4820515 A A23K 19890411 Texas A&M University System
Method of using interferon in low dosage to regulate appetite and efficiency of food utilization

89. US4824432 A A61M 19890425 SS. Laboratories, Inc.
Method for treating AIDS and other immune deficiencies and immune disorders

90. US4820638 A C07K 19890411 Dr. Karl Thomae GmbH
Novel alpha interferon species produced by recombinant means

91. US4791101 A A61K 19881213 Boehringer Ingelheim
Synergistic mixtures of interferons and tumor necrosis factor

92. US4765903 A A61K 19880823 Interferon Sciences, Inc.
Purification of monomeric interferon

93. US4743445 A A61K 19880510 Boehringer Ingelheim International GmbH
Method for treatment of essential (hemorrhagic) thrombocythemia

94. US4732683 A C07K 19880322 BioSpectrum, Inc.
Purification method for alpha interferon

Claim 1: . A method of purifying interferon alpha comprising the steps;
(a) loading a crude interferon alpha solution to a glass sorbent chromatography;
(b) eluting interferon alpha from the glass sorbent with a first hydrophobic electrolyte solution having a pH ranging from about 6 to about 9;
(c) loading the eluate of step (b) to a molecular sieving chromatography having a resolution capacity of about 10,000 to about 100,000 molecular weight;
(d) developing the molecular sieve with a second hydrophobic electrolyte solution and collecting the eluate corresponding to a molecular weight ranging from about 10,000 to about 40,000; and
(e) loading the collected eluate of step (d) to a Zn++ chelate resin and collecting the non-adsorbed flow through eluate, which contains purified interferon alpha.

95. US4696899 A C12P 19870929 EGYT Gyogyszervegyeszeti Gyar
Process for the preparation of human leukocyte and human gamma interferon

96. US4680260 A C12N 19870714 Vsesojuzny Nauchno Issledovatelsky Institut Genetiki
Method for producing human leukocyte interferon alpha-2

97. US4675282 A G01N 19870623 Damon Biotech, Inc.
Assay for interferon epsilon

Claim 1: An interferon preparation having antiviral activity, said preparation being characterized in that:
(i) it is made by a living cell containing a gene active in human epithelial cells;
(ii) its antiviral activity is specific to human epithelial cells;
(iii) it is antigenically distinct from **interferon alpha**, interferon beta, and interferon gamma;
(iv) its antiviral activity is stable at pH 2 and is destroyed by proteolytic enzymes; and
(v) it has no detectable antiviral activity in human fibroblast cells.

98. US4636383 A A61K 19870113 Schering Corporation
Interferon-cyclaradine combination

99. US4618494 A A61K 19861021 Immunology Development Corporation
Human Immune Factors and processes for their production and use

100. US4614651 A A61K 19860930 Damon Biotech, Inc.
Interferon epsilon

101. US4496537 A A61K 19850129 Schering Corporation
Biologically stable alpha-interferon formulations

Claim 1: In a method for preparing a formulation of high specific activity **alpha-type interferon** having improved biological stability by lyophilizing a solution containing said alpha-type interferon to yield a reconstitutable lyophylizate, the improvement for further increasing said biological stability to a level such that the lyophilizate substantially retains its biological activity even when stored at 20° C. for at least six months which comprises: adding to said solution prior to lyophilization (a) a compatible buffer which will maintain the pH of the reconstituted solution within the range of about 6.5 to 8.0, and (b) glycine or alanine in an amount of 5 to 150 milligrams per milliliter of water to be added for reconstitution

102. US4469228 A A61K 19840904 Schering Corporation
Interferon kit

Claim 1: A kit for formulating and dispensing an alpha type interferon gel composition comprising (a) a vial having an open end aseptically sealed and containing about 1×104 to 5×108 International Units of lyophilized **alpha type interferon** formulation prepared from an alpha type interferon having a specific activity of at least 5×107 International Units/mg total protein; (b) and a tube with flexible walls having a sealed open end containing a dermotologically acceptable vehicle which contains a compatible preservative and a sufficient amount of polyoxyethylene polyoxypropylene block polymer for the vehicle to be liquid at 15° C. or below and which together with the lyophilized alpha interferon gels at 15° C. and above.

103. US20010012514 A1 A61K 20010809 Advanced Biotherapy Concepts, Inc.
Treatment of autoimmune diseases, including AIDS

The above list includes issued patents the recite alpha interferon as an element in the claim; these patents go back as early as 1983. Exemplary claims show that the patents recite alpha interferon as an element. Hence, those of skill in the art in 2001 would understand what is meant by the term "alpha interferon." As noted above, one of skill in the art would then readily be able to ascertain whether a particular alpha interferon includes a Q at residue 41.

2. Claim 6 is alleged to indefinite because is not clear if the "one or more mutations mentioned in claim 1 are the mutations selected from the list in claim 6 or a totally new set of mutations."

Amendment of the claim renders this ground of rejection moot.

3. Claim 7 is rejected as indefinite in the recitation of "human."

Amendment of the claim renders this ground of rejection moot.

4. Claim 17 is rejected as indefinite in the recitation of "replication" claims 18, 315 and 339 are indefinite because it is unclear if the antiviral activity of the mutant is compared with the anti-proliferative activity of the unmodified cytokine or if the comparison is actually made between the respective ratios of antiviral/antiproliferative activities of the mutant and the unmodified cytokine. Claims 332-335 also are rejected as indefinite.

Cancellation of claims 17, 18, 315, 332-335 and 339 herein renders these grounds for rejection moot.

5. Claim 279 is indefinite because the meets and bound of "an interferon alpha structural homolog" cannot be assessed. This rejection is respectfully traversed.

The application is directed to methods for directed evolution of proteins, and particularly the method in which mutations are identified in an exemplary protein and then based upon the 3-D structure of related polypeptides, the corresponding mutation is introduced into other family members. The instant application describes preparation of interferon alpha-2b mutants that exhibit increased resistance to proteases and then describes

how structural homology can be used to identify the corresponding mutation in all cytokines. The application provides about 1300 exemplary modified structural homologs. For example, at pages 70-71 the specification states:

> Also provided herein is a method of structural homology analysis for comparing proteins regardless their underlying amino acid sequences. For a subset of proteins families, such as the family of human cytokines, this information is rationally exploited herein. Human cytokines all share a common helix bundle fold, which is used to structurally define the 4-helical cytokine superfamily in the structural classification of the protein database SCOP© (Structural Classification of Proteins; see, e.g., Murzin et al., J. Mol. Biol., 247:536-540, 1995 and "scop.mrc-lmb.cam.ac.uk/scop/"). This superfamily includes three different families: 1) the interferons/interleukin-10 protein family (SEQ ID NOS: 1 and 182-200); 2) the long-chain cytokine family (SEQ ID NOS: 210-217); and 3) the short-chain cytokine family (SEQ ID NOS: 201-209).
>
> For example, a distinct feature of cytokines from the interferons/interleukin-10 family is an additional (fifth) helix. This family includes interleukin-10 (IL-10; SEQ ID NO:200, interferon beta (IFNβ; SEQ ID NO: 196), interferon alpha-2a (IFNα-2a; SEQ ID NO: 182), interferon alpha-2b (IFNα-2b; SEQ ID NO:1), and interferon gamma (IFN-γ; SEQ ID NO: 199). The long-chain cytokine protein family includes, among others, granulocyte colony stimulating factor (G-CSF; SEQ ID NO: 210), leukemia inhibitory factor (LIF; SEQ ID NO: 213), growth hormone (hGH; SEQ ID NO: 216), ciliary neurotrophic factor (CNTF; SEQ ID NO: 212), leptin (SEQ ID NO: 211), oncostatin M (SEQ ID NO: 214), interleukin-6 (IL-6; SEQ ID NO: 217) and interleukin-12 (IL-12; SEQ ID NO: 215). The short-chain cytokine protein family includes, among others, erythropoietin (EPO; SEQ ID NO: 201), granulocyte-macrophage colony stimulating factor (GM-CSF; SEQ ID NO: 202), interleukin-2 (IL-2; SEQ ID NO: 204), interleukin-3 (IL-3; SEQ ID NO: 205), interleukin-4 (IL-4; SEQ ID NO: 207), interleukin-5 (IL-5; SEQ ID NO: 208), interleukin-13 (IL-13; SEQ ID NO: 209), Flt3 ligand (SEQ ID NO: 203) and stem cell factor (SCF; SEQ ID NO: 206).
>
> Although the degree of similarity among the underlying amino acid sequences of these cytokines does not appear high, their corresponding 3-dimensional structures present a high level of similarity (see, e.g., FIGS8B through D). Effectively, the best structural similarity is obtained between two 3-dimensional protein structures of the same family in the 4-helical cytokine superfamily.
>
> The methods provided herein for producing mutant cytokines are exemplified with reference to production of cytokines that display a substantially equivalent increase in resistance to proteolysis relative to the optimized IFNα-2b mutants. It is understood that this method can be applied to other families of proteins and for other phenotypes.

The detailed description section of the application includes an entire section that describes structural homologs of interferon alpha-2b (pages 74-76):

> **a. Structurally Homologous Interferon Mutants**
>
> Also provided herein are modified cytokines or cytokine structural homologues of IFNα-2b that are IFNα cytokines. These IFNα cytokines include, but are not limited to, IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8 and IFNα-consensus cytokine (see, SEQ ID No. 232). Accordingly, among the modified IFNα cytokines provided herein are those with one or more amino acid replacements at

one or more target positions in either IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, or IFNα-consensus cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNα-2b modified proteins provided herein. The replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-2a.

In particular embodiments, the modified IFNα cytokines are selected from among:

the modified IFNα-2a that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 182, corresponding to amino acid positions: 41, 58, 78, 107, 117, 125, 133 and 159;

the modified IFNα-c that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 183, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the modified IFNα-2c cytokine that is human and is selected from among cytokines comprising one or more single amino acid replacements in SEQ ID NO: 185, corresponding to amino acid positions: 41, 58, 78, 107, 117, 125, 133 and 159;

the IFNα-d modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 186, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-5 modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 187, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-6 modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 188, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-4 modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 189, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-4b modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 190, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-I modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 191, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-J modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 192, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-H modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 193, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-F modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 194, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160;

the IFNα-8 modified protein that is human and is selected from among proteins comprising one or more single amino acid replacements in SEQ ID NO: 195, corresponding to amino acid positions: 41, 59, 79, 108, 118, 126, 134 and 160; and

the IFNα-consensus modified protein that is human and is selected from among proteins that contain one or more single amino acid replacements in SEQ ID NO: 232, corresponding to amino acid positions: 41, 58, 78, 107, 117, 125, 133 and 159.

Hence when read in light of the specification, the meaning of "an interferon alpha structural homolog" is clear.

6. Claim 341 is indefinite in the recitation of "comprising only."

As amended the claim recites that the interferon alpha only contains an E41Q replacement compared to the unmodified interferon that does not include the E41Q replacement, thereby obviating this ground for rejection.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 5-7, 16-19, 21-23, 40, 43, 44, 139, 141, 279, 307-308, 315, 316 and 332-347 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 68-70, 72-79, 81-82 84-86, 89-90 of copending Application No. 11/176,830. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to proteolytic resistant Interferon variants or compositions containing the same.

Because the instant application and the copending application are in prosecution, and the claims in one or both of the applications may be amended, it is premature to file a terminal disclaimer. The copending application includes generic claims to compositions formulated for oral administration that contain cytokines modified in their primary sequence, whereby the cytokine is protease resistant. Dependent claims recite that the cytokine is an interferon alpha. The possibility for obviousness-type double patenting in the instant application and the copending application only exists with respect to these dependent claims. If claims in the instant case, which are directed to interferon alpha cytokines with a modification at E41Q (or the corresponding locus), are allowed, claims to this family may be cancelled in the copending application voiding the need for terminal disclaimer in the instant application. Accordingly deferral of resolution of this issue respectfully is requested.

THE REJECTION OF CLAIMS 1, 5, 6, 16-18, 19, 21-22, 40, 43, 44, 139, 141, 307, 308, 315-316, 332-340 AND 343 UNDER 35 U.S.C. §102(b)

Claims 1, 5, 6, 16-18, 19, 21-22, 40, 43, 44, 139, 141, 307, 308, 315-316, 332-340 and 343 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Testa *et al.* (U.S. Patent No. 5,676,942). Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks and the remarks of record.

The remarks and arguments in the previous response are incorporated by reference. Testa *et al.* does not disclose any isolated interferon alpha cytokines that possess increased protease resistance compared to the unmodified form thereof. Applicant does not concede that the rejection is apt with respect to any of the rejected claims as previously pending. Nevertheless, as noted the claims are amended in order to advanced claims to issuance. As amended all claims require that the modified alpha interferon include a replacement of E with Q at residue 41. Testa *et al.* does not disclose any interferon alpha polypeptide that includes such modification. Therefore, Testa *et al.* does not anticipate any pending or rejected claim.

THE REJECTION OF CLAIMS 1, 6, 7, 23, 279, 307-308, 315, 316, 341, 342 AND 344-347 UNDER 35 U.S.C. §103(a)

Claims 1, 6, 7, 23, 279, 307-308, 315, 316, 341, 342, and 344-347 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinrichs *et al.* (WO 01/25438 in view of Blank *et al.* (Eur. J. Biochem., 265, 11-19, 1999) and in further view of Jensen *et al.* (WO/01/36001, 05/25/2001) and Sheppard P. (U.S. Pat. 6,153,420). This rejection is directed to claims insofar as they recite that the modification is E41Q. The Examiner urges: Heinrichs *et al.* teaches interferon-alpha homolog polypeptides that are designed towards optimization for use as pharmaceuticals and to overcome dose-limiting toxicity, receptor cross-reactivity and short serum half-lives creating "an opportunity for the construction of superior interferon homologues;" Blanks *et al.* teaches "possible cleavage sites for the IFN α-2b molecule" that include the E41; Jensen *et al.* teaches "the introduction of E38N glycosylation site in IFN-gamma, to obtain a protease resistant mutant for a position of the residues, which exposed at least 50% to the surface of the polypeptide (p. 16, line 32 to p.17, line 2)," which. constitutes "a potential cleavage site for proteases like Glu-C"; and Sheppard teaches a mutant "serine protease homologous to glutamyl endopeptidases which are found in tissues exposed to the external environment, like small intestine and colon (col. 5, line 21, to col. 6, line 31)." The Examiner concludes that:

> [i]t would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the methods of Heinrichs to mutate the interferon a-2b at E41 to confer the mutant increased resistance to Glu-C protease with a

> reasonable expectation of success. The motivation to do so would have been suggested by Heinrichs et al namely to improve the serum half-life and stability. Further combination of the teachings of Heinrichs et al. and Blank et al. with the teachings of Jensen et al. would have assured that the mutant thus obtained is resistant to proteases like the ones described by Sheppard especially if the Interferon mutant is formulated for oral use and resistance against Glu-C endopeptidases would be essential.

This rejection respectfully is traversed.

Relevant Law

To establish prima facie obviousness under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 USPQ. 43 (CCPA 1963). Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). See also KSR, 127 S.Ct. at 1734, 82 USPQ2d at 1391 ("While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.") The Court in Graham noted that evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., "might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." 383 U.S. at 18, 148 USPQ at 467. Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact

finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. Id. at 1740-41, 82 USPQ2d at 1396 (citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. The court stated in dicta that, where there is a "market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try **might** show that it was obvious under § 103."

In a post-KSR decision, PharmaStem Therapeutics. Inc. v. ViaCell. Inc., 491 F.3d 1342 (Fed. Cir. 2007), the Federal Circuit stated that:

> an invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Furthermore, KSR has not overruled See In re Papesch, (315 F.2d 381, 137 USPQ 43 (CCPA 1963)), In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991), and In re Deuel (51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995)). "In cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007).

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or

combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

As always, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). It appears that the Office Action has combined the teachings of the prior art with those of the instant application.

The Rejected Claims

The pending claims are directed to modified interferon alpha cytokines that contain replacement of residue E41 with Q (or the corresponding residue based on alignment, where the sequence may differ in length by a residue or two). Dependent claims also recite compositions that contain such cytokines. Claim 345 is directed to an interferon alpha cytokine that has a sequence of amino acids set forth in SEQ ID NO:87.

Differences between the cited references and the claims

Heinrichs *et al.* (WO 01/25438)

Heinrichs *et al.* describes methods for identifying IFN-α homologs having altered properties or activities using sequence recombination, such as DNA shuffling, to produce a diverse set of recombinant nucleic acids that can be screened or selected for a desired activity. Heinrichs *et al.* teaches that the method can be used to select for nucleic acids having enhanced antiviral, antiproliferative, growth inhibitory, cytostatic, cytotoxic activity or reduced immunogenicity, or other property such as low immunogenecity, increased half-life, improved solubility or oral availability. Henrichs *et al.* teaches IFN-α homolog that were discovered in libraries of shuffled IFN-α species from 20 human IFN-α subspecies genes. Resulting clones were assayed for antiproliferative and antiviral activity to identify

those with the highest activity in *in vitro* and *in vivo* assays. Henrichs *et al.* also teaches that the **resulting** polypeptides can be **further** modified, for example, to increase serum half-life, reduce antigenicity, or increase polypeptide stability and teaches that such modifications include a glycosylated amino acid, a sulfated amino acid, a prenylated amino acid, an acetylated amino acid, an acylated amino acid, a PEG-ylated amino acid, a biotinylated amino acid, a carboxylated amino acid, and a phosphorylated amino acid. Thus, Henrichs *et al.* teaches a directed evolution method by which one could identify interferon mutants that have enhanced antiviral, antiproliferative, growth inhibitory, cytostatic, cytotoxic activity or reduced immunogenicity, or having other property such as low immunogenicity, increased half-life, improved solubility or oral availability. Henrichs *et al.* does not teach or suggest modifying a protein to render it protease resistant by a change in primary sequence.

Henrichs *et al.* does not teach or suggest modifying any protein to have increased resistance to any protease nor does Henrichs *et al.* teach or suggest an IFN-α homolog that exhibits increased protease resistance, nor modification of an IFN-α species or an IFN-α homolog to render it more resistant to proteases. Henrichs *et al.* does not teach or suggest the modification E41Q, nor any modification specifically identified in the instant application to increase resistance to proteolysis. Henrichs *et al.* does not teach or suggest that modification of an interferon-alpha would improve it pharmacokinetics upon subcutaneous administration nor render it active upon oral administration.

Blank *et al.*

Blank *et al.* does not cure the deficiencies in the teachings of Henrichs *et al.* Blank *et al.* is directed to the identification of epitopes in IFN-α2b that confer binding to four different anti-IFNα2b monoclonal antibodies, including identification of the sequence recognized by the antibodies by comparing the immunoreactivity of various proteolytically digested fragments. To the extent Blank et al. teaches anything related to proteases, Blank et al. teaches the ***possible*** cleavage sites in IFN-α2b following digestion with Arg-C (C-terminal end or arginine residues), Glu-C endoprotease (C-terminal end of glutamate residues) and prolyl endopeptidases (C-terminal end or proline residues.) Specifically, Blank *et al.* teaches that *any* glutamic acid (E) is a potential cleavage site for Glu-C, *any* arginine (R) is a potential cleavage site for Arg-C and *any* proline (P) is a potential cleavage site for prolyl endopeptidases in the amino acid sequence of IFNα2b (see Figure 5). Since position 41 in the amino acid sequence of IFNα2b is Glu (E), it was identified as a ***possible*** cleavage site by Glu-C endoprotease. Following digestion with each of the proteases, however, Blank et al.

identified **actual cleavage sites** based on N-terminal sequencing of corresponding digested fragments. ***Glu41 is not among the sites identified as cleavage sites.*** Rather, Blank *et al.* **Glu42** is identified as a cleavage site. Hence, Blank et al. cannot and does not teach that Glu41 is a protease cleavage site in any IFN-α molecule.

Notwithstanding this failure, Blank et al. does not teach or suggest any modification if any interferon, and certainly not at position 41 of any interferon α, nor any modification of any interferon, including IFN-α2b, to render it resistant to proteases. Thus, Blank *et al.* does not cure the deficiencies in the teachings of Henrichs *et al.*

Jensen *et al.*

Jensen et al. teaches **interferon-gamma** polypeptide **conjugates**, and compositions containing such conjugates. The conjugates are prepared by modification of IFN-gamma polypeptides to include an attachment site to link a non-polypeptide moiety, such as a PEGylated moiety, to the polypeptide. It is the conjugates, **not the polypeptides,** that exhibit improve stability towards proteolysis. Among the conjugates taught by Jensen et al. are conjugates that contain an altered glycosylation by introduction or removal of glycosylation sites. For example, Jensen et al. teaches introduction of additional N-glycosylation sites by modification of the IFN-gamma polypeptide to create an in vivo glycosylation site. Jensen et al. teaches that N-glycosylation sites are created at sites exposed to the surface, such that 25%-50% of the side chain is exposed. Jensen et al. further teaches that it is preferable to create N-glycosylation sites where only one amino acid residue is required for creating a functional glycosylation site, though most modifications taught in Jensen et al. require more then one modification such that two amino acids removed from the introduced N glycosylation site is a serine (S) or threonine (T) moiety. Among the modifications in interferon gamma where only one amino acid modification is required to introduce an N-glycosylation site is E38N (since position 40 of the polypeptide contains a serine (S), see e.g., SEQ ID NO:2). Jensen et al. teaches that conjugates of the interferon with glycosylation moieties may exhibit increased stability to proteases. Jensen et al. further teaches administration of conjugates by any of a variety of routes of administration, including oral administration, but does not suggest that modification of a protein in it primary sequence to increase protease resistance permits oral administration. There is nothing in the art that would suggest the proteases in the gut or serum or elsewhere would not cleave other sites.

Jensen et al. teaches the introduction of E38N glycosylation site in IFN-gamma in order, **with the adjacent residues,** to create **a glycosylation site**. Glycosylation is believed

protecting the polypeptide to which the glycosylation moiety is attached by virtue of its preferential degradation, not because a protease cleavage site is modified. Jensen *et al.* does not teach or suggest modifying the primary protein to render it resistant to proteases by virtue of the modification; Jensen *et al.* requires introduction of glycosylation site. Jensen *et al.* teaches that the E residue changed should be adjacent to other residues required for glycosylation (NX(S or T) . **E41 in interferon-alpha is not such a site (residue 43 is not T or S).**

Jensen et al. does not teach or suggest modified cytokines that exhibit increased protease resistance compared to an unmodified cytokines because Jensen et al. is directed to conjugates, not polypeptides. Jensen *et al.* teaches modification of interferon gamma for attaching glycosylation moieties. Jensen *et al.* does not teach or suggest modifying the interferon gamma so that the polypeptide exhibits increased resistance to proteases. Jensen *et al.*, provides no teachings or suggestions regarding modification of the primary sequence of any interferon alpha, of increased protease resistance can be administered orally and rendered orally available.

Sheppard *et al.*

Sheppard *et al.* is directed to a serine protease, Zsig13, which was identified by querying an EST database. Sequence analysis revealed homology to serine proteases, and sequence alignment with other proteases confirmed this. Probing of tissue samples indicates that this protease is a expressed in the trachea, bladder, small intestine, colon and prostate. Sheppard *et al.* states that this data suggest that it could be a digestive or anti-bacterial protease. Sheppard *et al.* does not teach or suggest that modifying a protein to be resistant to this putative digestive or bacterial enzyme nor that rendering a protein resistant thereto would render a protein, previously inactive upon oral administration, active, nor that it would improve the pharmacokinetics upon subcutaneous administration. Sheppard *et al.* states that potential utility of Zsig13 is to degrade unwanted proteins in industrial processes. Sheppard *et al.* provides not teachings or suggestions that are of any relevance to the instant claims. Sheppard *et al.* provides no teachings or suggestions for modification of interferon-alpha by replacing E41 with Q. Thus, Sheppard *et al.* does not cure the deficiencies in the teachings of any of Heinrich *et al.*, Blank *et al.* Jensen *et al.*, singly or in combination.

The combination of teachings of Heinrich *et al.* with those of Blank *et al.*, Jensen *et al.*, and Sheppard *et al.* do not result in any of the instantly claimed subject matter.

The law does not hold that if one wanted to invent what applicant has invented they would have tried all combinations and eventually would have invented it. Such standard could never be met. In this instance, the Applicant has made a truly valuable and significant discovery, that would not result from the teachings or suggestions of any of the cited references, singly or in any combination thereof. There is no teaching or suggestion in the cited art of record to render proteins protease resistant; there is no teaching or suggestion to do so with interferon alpha, there is no teaching or suggestion regarding sites to modify; there is no teaching or suggestion that rendering a protein more resistant to proteases renders them suitable for oral administration; there is no teaching or suggestion that modifying a single amino acid residue results in a protein that can be administered orally and that has improved pharmacokinetic upon subcutaneous administration, and retains the relevant biological activity of the protein that does not contain such modification. Further none of the art teaches or suggests an interferon alpha in which residue 41 is changed from E to Q. "In cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007).

None of the references teaches or suggests (1) modifying any polypeptide to render it protease resistant; nor (2) modifying an interferon α at position 41 or at a position corresponding thereto. Blank *et al.* teaches that Glu42 is a protease cleavage site; Jensen *et al.*, which is directed to interferon gamma conjugated to a non-protein moiety, teaches that introduction of a glycosylation site should be effected a site where the next residues are X(S or T); Glu41 does not meet this requirement.

Thus, the combination of teachings of the references cannot teach modification of any interferon α to render it more resistant to a proteases than the unmodified proteases, nor can the combination of teachings teach modification of an interferon α by replacing the amino acid at a position corresponding to E41 with a Q.

Specifically, combination of teachings of Heinrich *et al.* with those of Blank *et al.*, Jensen *et al.*, and Sheppard *et al.*, fails to teach or suggest an interferon alpha cytokine that contains an amino acid replacement corresponding to E41Q, or any other amino acid replacement, conferring increased resistance of the cytokine to proteolysis compared to the

unmodified cytokine not containing the mutation. There is no teaching or suggestion in any cited reference. that an interferon alpha cytokine can be modified to have increased protease resistance compared to the unmodified cytokine not containing the amino acid replacement. None of the cited references, singly or in combination teaches or suggests replacing E41 with Q. Therefore, the combination of teachings of Heinrichs *et al.*, Blank *et al.*, Jensen *et al.*, and Sheppard *et al.*, does result in the instantly claimed subject matter. The Examiner has failed to set forth a *prima facie* case of obviousness.

Notwithstanding the above, the attached Declaration of Dr. Vega demonstrates results not taught or suggested by the combination of teachings of the cited references.

Notwithstanding the fact that the combination of teachings of the references fails to teach or suggest modifying a polypeptide to increase protease resistance, the combination of teachings of the reference does not teach or suggest the results achieved thereby. These results include: (1) increased resistance to protease does not require modification of all protease cleavage sites; (2) modification can be achieved without substantially altering a desired biological activity; (3) polypeptides, which are not orally available, become so upon modification to exhibit increased protease resistance; and (4) the polypeptides modified to be exhibit increased resistance to proteases also exhibit improved pharmacokinetics upon subcutaneous administration.

These results are described in the application, and also demonstrated in the Declaration of Dr. Manuel Vega, a joint inventor, previously provided and again discussed below. The application, and Declaration, describe that a cytokine, including an interferon alpha cytokine, exhibiting increased resistance to proteolysis, when administered subcutaneously or orally, exhibit increased stability and half-life and thus exhibit improved pharmokinetics compared to a cytokine not containing the modification. None of the cited references, singly or in any combination teaches or suggests such results.

As discussed, Blank *et al.*, concludes that Glu42 is a protease cleavage site; Jensen is directed to interferon-gamma conjugates and teaches that for preparation of a conjugate a replaced Glu should be followed by X(S or T); and Sheppard *et al.* teaches a putative protease identified from an EST library that may be expressed in the digestive tract. Sheppard *et al.* (nor any cited reference) does not teach or suggest that rendering a protein resistant to this proteases or any glutamyl endopeptidase would permit oral administration of such protein. Sheppard *et al.*, nor any cited reference, does not teach or suggest that these are the only proteases present in the gut. Further, the instantly modified interferon-alpha proteins

exhibit improved pharmacokinetics upon subcutaneous administration . Modification of E41 does not result in a loss of relevant biological activity.

DECLARATION

The DECLARATION of Dr. Manuel Vega demonstrates that the interferon alpha cytokines exhibit properties not taught or suggested by the cited references nor any references of record. The DECLARATION demonstrates: (1) increased resistance to protease does not require modification of all protease cleavage sites; (2) modification can be achieved without substantially altering a desired biological activity; (3) polypeptides, which are not orally available, become so upon modification to exhibit increased protease resistance; and (4) the polypeptides modified to be exhibit increased resistance to proteases also exhibit increase serum stability and half-life.

In particular, the DECLARATION shows that modification of as few as a single residue (see Table 1), such as E41Q, results in a polypeptide that exhibits increased protease resistance. Such resistance is not necessarily resistance to a particular protease, but to a variety of proteases. The DECLARATION demonstrates that when modified based on the property of increased protease resistance, exhibit increased resistance to proteases *in vitro* and *in vivo*. For example, as described in the application and as provided in the DECLARATION, exemplary candidate LEAD polypeptides tested for proteolysis against a cocktail of proteases *in vitro* exhibited increased proteolysis compared to an IFNα-2b not containing the modification.

The DECLARATION also demonstrates that the resulting modified cytokines can retain original activity. As described in the DECLARATION, the results show that the exemplary mutant E41Q IFN-α2b not only exhibits increased protease resistance to a **cocktail of proteases, and** also to **blood lysate, serum and to chymotrypsin**. Thus, the amino acid replacement confers increased protease resistance of the cytokine across the entire molecule, which increased resistance is **not specific to a particular protease**. None of the cited references teaches or suggests such result.

In the DECLARATION, data also are provided that demonstrate that the proteins exhibit improved pharmacokinetics upon subcutaneous and oral administration compared to proteins not containing the amino acid replacement(s). For example, the DECLARATION provides data demonstrating that a mutant IFN-α containing E41Q, when administered subcutaneously or orally, retains anti-viral activity in the serum for a longer time period than the native polypeptide. In addition, the result show that SuperLEADs, containing two or

more amino acid changes described in the above-captioned application, also exhibit similar increases in half-life. .

In the case of per-oral administration, the native polypeptide retains **no** detectable activity when administered; whereas, the IFN-α with the E41Q change, can be successfully administered orally. For example, Figure 3 shows that unmodified interferon alpha cannot be adminstered orally; whereas, the modified form can be administered orally **and** exhibit anti-viral activity in the serum. *This really is astounding*, and of enormous medical and economic value. Therefore, the results provided in the DECLARATION show that the interferon alpha cytokines as claimed have properties that are not taught or suggested by any of the cited references.

None of the cited references, singly or in any combination thereof, teaches or suggest modifying the cytokine by amino acid replacement(s) to render the molecule resistant to proteases, nor teaches any of the modifications described in the application, including E41Q. None teaches or suggests that a polypeptide having increased protease resistance would exhibit increased half-life and stability upon subcutaneous or per-oral administration. None of the cited references, singly or in any combination, teaches or suggests that modification to render a polypeptide protease resistant, renders a polypeptide, that had not been orally available, suitable oral administration. Therefore, the claims cannot be obvious in view of the cited references.

Furthermore, to combine these references to result in the instant claims relies on the improper use of hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The Examiner urges that it would have been obvious to use the methods of Heinrichs *et al.* to mutate IFNα to confer the mutant with increased protease resistance, and to do so would have been suggested by Heinrichs *et al.* which lists improved serum half-life and stability as among properties of proteins to evolve. Henrichs *et al.*, however, does not mention protease resistance as among those properties nor that such would increase serum half-life and stability. The Examiner points to Blank *et al.* as suggesting modification of E41Q as a site for modification. In fact, Blank *et al.* concludes that the actual cleavage site I

E42. Jensen *et al.* is cited to somehow suggest that one can modify proteins to increase protease resistance. Jensen *et al.* teaches interferon-gamma- conjugated to a non-protein moiety that confers protease resistance. As discussed above, Jensen *et al.* teaches that creation of a glycosylation site requires selection of a residue that is next to X(S or T). E41 is not such a residue. The Examiner sits Sheppard *et al.* as somehow suggesting that resistance to Zsig13 would render a protein orally available. Nothing in Sheppard *et al.* suggests anything such, nor is it likely (nor is there any art of record that suggests) that resistance to a single protease would render a protein orally available. As shown in the application and DECLARATION interferon alpha with the E41Q modification is resistant to a cocktail of proteases as wells as various serum and other proteases.

Thus, the only way the Examiner can combine the teachings of the cited references is to rely on the instant application as guide for selecting the references and modifying their teachings. The cited references must provide some teaching or suggestion to do that which applicant has done. This is absent in the instant case.

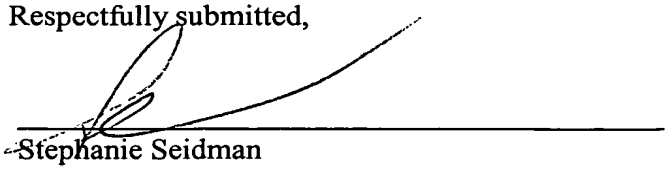
Therefore, for any and all of these reasons, the Examiner has failed to set forth a *prima facie* case of obviousness.

The undersigned respectfully states that the Office in its diligence to avoid issuing unwarranted patents, should not be over zealous in rejecting all claims. To do so is stifling to industry and will destroy struggling early stage and emerging companies with truly innovative products. This is one such case. Applicant respectfully requests reconsideration and withdrawal of this rejection.

* * *

In view of the above, examination of the application on the merits and allowance are respectfully requested.

Respectfully submitted,



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APPENDIX

Attached are:

1. Figure depicting sequence alignment of IFN-alpha polypeptides;
2. Annotated paper copy of SEQ ID NO:232;
3. Replacement Sequence Listing on compact disc (labeled Replacement Copy #1 and Replacement Copy #2);
4. Computer-readable copy of substitute Sequence Listing; and
5. Verified Statement Pursuant to §1.821(f).